**U.S. FOOD AND DRUG ADMINISTRATION**

**Center for Drug Evaluation and Research (CDER)**

# ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVAC) MEETING

## Clinical Trial Design Issues in the Development of Topical Microbicides for the Reduction of HIV Transmission

**20 August 2003**

**Holiday Inn - Versailles Ballroom - 8120 Wisconsin Avenue -Bethesda, MD 20914**

**PRESENTATION TO THE**

**OPEN PUBLIC HEARING**

**on behalf of the**

***Ad Hoc* Subcommittee of the Alliance for Microbicide Development**

***(submitted* a priori *as written public comment)***

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## Introduction

**This presentation addresses core issues in microbicide clinical trial design that have been under consideration by an *Ad Hoc* Subcommittee of the Alliance for Microbicide Development since the Alliance "Mini-Summit on Clinical Trials" held in March in Washington, DC *(see Appendix A for Subcommittee roster)*. The Subcommittee does not presume to speak for "the microbicide field" as some sort of organized whole, but finds that it represents substantial consensus across that field. Some of that consensus will be reiterated in other individual formal presentations and written comments provided to the Antiviral Drugs Advisory Committee, as will, of course, any significant divergence of opinion.**

**We wish to note that the discussions that led to the writing and subsequent review of this document were completed before the FDA's *Briefing Information* document was posted on the agency's web site. However, the two documents do correspond in their overall focus and emphases on the major components of microbicide clinical trial design.**

## The Fundamental Issue: The Need for Microbicides

***A Large Global Population at Particular Risk.*** The increasing intensity of focus on topical microbicides emerged largely from the recognition that HIV/AIDS increasingly has a "woman's face"[1]. Worldwide, almost half of the 37.2 million adults living with HIV/AIDS at end-2002 were female and, of the 5 million new infections in that year, 40% were in women. Those percentages are even higher in sub-Saharan Africa, where for every 10 African men, 12-13 African women are infected.[2] In the United States, the proportion of AIDS cases among women has more than tripled since 1986, rising from 7% to 23% by 2002.[3] In sum, HIV transmission is now overwhelmingly heterosexual, such that the greatest source of risk of HIV for a woman in a developing country is likely to be her husband.[4] Women—especially young women—are further vulnerable, since they are biologically far more susceptible than men to sexually transmitted infections other than HIV, many of which enhance the sexual transmission and progression of HIV, in some instances by a factor of up to 10.[5]

Yet research indicates that many women in many geographic and sociocultural settings are reluctant or unable to talk with their partners about use of condoms, the one existing preventive technology offering reasonable protection against sexually transmitted infections (STIs). This is true in both developed- and developing-country settings, and notably true for women disadvantaged by economic dependence, poverty, and gender discrimination who cannot risk their relationships by questioning partner fidelity.[6] Consistent condom use has been found universally hard to achieve in stable relationships, and there are few examples over 20%; even individuals willing to use condoms with "outside" partners appear unwilling or unable to use them with a primary, stable partner. Further, in cultures where childbearing is linked to self-worth and societal position, the prospect of childlessness often outweighs considerations of risk.[7]

***The Potential Value of Microbicides.*** Microbicides, as an innovative preventive technology whose use need not depend on partner cooperation or even knowledge, would offer women for the first time the ability to determine their own protection. A major modeling exercise by the London School of Tropical Medicine and Hygiene found that a 60% efficacious microbicide used by 20% of women in 73 lower-income countries (including all of sub-Saharan Africa) in 50% of sex acts where condoms were not used would avert 2.5 million HIV infections over three years in women, men, and children, saving $2.7 billion in health care costs and $1 billion in lost productivity.[8] These savings estimates are probably modest: according to the recently-issued UNDP *Human Development Report*, 54 countries are now poorer, 21 countries have worse hunger problems, and 34 have experienced declines in life expectancy since 1990, primarily because of HIV/AIDS.[9]

The potential of microbicides as a new preventive technology is further promoted by the fact that the search for an HIV vaccine, which would theoretically protect both males and females, is proving far more complex than anticipated, and remains a distant possibility.[10] This means that microbicides could be, at a minimum, a critical preventive technology for what may be a long interim period until an HIV vaccine materializes. Even after that, since microbicides and vaccines will each provide only partial protection, a strong argument can be made for them both as complementary preventive technologies, particularly in the case of microbicides offering a broader spectrum of protection against different HIV clades and any non-HIV STIs or vaginal infections acting as co-factors for HIV transmission.[11] It may well be, in fact, that microbicides and/or vaccines that could elicit durable mucosal immunity, thus targeting the earliest stages of HIV infection, might offer the best prospects for preventing or containing HIV infection.[12]

## Background Issues

The Subcommittee recognizes and honors the FDA's mandate to protect the health and safety of the US population. However, that mandate is challenged in several ways by drug products—with microbicides the present case in point—whose main objective is to combat life-threatening diseases whose predominant weight falls on populations beyond US borders. These diseases include not only HIV/AIDS but the other major global killers, malaria and tuberculosis, as well as "other neglected diseases" primarily affecting developing countries and "emerging infectious diseases" that may or may not represent direct risks for US populations.[13]

First, such products typically fail to attract the involvement of "Big Pharma", so that their development becomes a patchwork effort across the public, nonprofit, and biotechnology sectors which can generate inefficiencies that may confound, or be especially confounded by, regulatory processes.

Second, the bulk of clinical testing of these products must by definition take place outside the United States in putative "countries of use", at the same time that, for epidemiological, ethical, and/or regulatory reasons, at least some trials may need to take place among at-risk populations in the United States as the "country of origin."[14] This "globalization of clinical trials"[15] raises ethical and practical dilemmas for product sponsors, protocol designers, trial implementers, and regulators, in the United States and in countries of use. At the top of the list of practical dilemmas may be the demand that the growing number and size of clinical trials of preventive technologies will place on the capacity of low- and middle-income countries to support the conduct of such trials according to Good Clinical, Laboratory, and Manufacturing Practice standards.[16]

Third, FDA approval may be construed as the "gold standard" by regulatory authorities outside the United States, such that the agency acts as a gatekeeper for licensure in some countries even though its mandate is officially "US only" and even though, in some instances, the United States may be an uncertain market.[17]

Cutting across these factors are two others: (1) the urgency imposed on all areas of relevant research by the rapid escalation and expansion of the HIV/AIDS pandemic, and (2) the divergence between epidemiological risk-benefit ratios in countries of origin and those in countries of use.[18] The need for urgency should be obvious and has been acknowledged operationally by the FDA, whose pace of approval of new HIV therapeutics has accelerated dramatically; however, whether the mechanisms used to speed development of HIV therapeutics might fit the case of microbicides is unclear.[19] As a product category intended for continued use over time by "healthy" people for disease prevention, microbicides, like HIV vaccines, raise challenges for testing unlike the testing of products intended for those who are already ill.

What is also unclear yet utterly central is how regulatory processes can take into account the differences between the enormous volume of risk in the countries which, in the case of HIV/AIDS, bear roughly 95% of the burden of disease and corresponding risk, and the volume of risk in countries where the burden of the epidemic is considerably less.[20] The question here, for the FDA and the microbicide field, is how to act expeditiously while striking an appropriate balance among consummate scientific rigor, ethical treatment of human subjects, and what is realistically feasible and truly informative.

## Need for a Paradigm Shift

If we accept the foregoing issues as valid, then it becomes evident that some sort of "paradigm shift" is needed in the testing and approval of certain product categories for certain populations. Indeed, the dimensions of such a shift with respect to HIV vaccines are already under active consideration by the World Health Organization and the EMEA (European Agency for the Evaluation of Medicinal Products) in a process that includes representation from the FDA's Center for Biologics.[21]

**The position of the FDA to date with respect to microbicides has been to maintain flexibility and consider the new products in this new field on a case-by-case basis. We vigorously urge continuance of this position. The very fact of an evolving technology, the intrinsic differences between traditional therapeutic trials and trials of preventive technologies, continued limits on understanding of the correlates of protective immunity in HIV infection,[22] lack of validated surrogates for product efficacy, and the dominance of needs for offshore testing together recommend a regulatory posture that is persistently flexible. We applaud the agency in its search for clarity and its ongoing and present efforts to involve the wider community of microbicide research and advocacy in that search. At the same time, we respectfully submit that a regulatory strategy for Phase II/III studies that is unduly complex, demanding, and rigid may not be feasible in developing-country settings and could, in fact, compromise safety, data quality, ethical integrity, and research specificity. We argue for simpler studies that successively substitute data from multiple sources for what are presently assumptions, address only the major issues for worldwide**

**regulatory approval, provide a sound basis for Phase IV and/or post-market monitoring, and are doable at a reasonable level of confidence. Finally, we urge the leadership of the FDA and CDER to become active participants in the advancing dialogue on the particular challenges of developing pharmaceutical products for developing-country populations.**

In the spirit of this argument, we offer the following observations, presented according to what we agree to be the strengths and limitations of each major element in the design of clinical trials to evaluate product effectiveness. We agree that trials must be large enough to ensure sufficient HIV end-points to provide a robust, statistically significant result; that enrollment must occur at various sites where there is a high incidence of new HIV infections; that bridging studies in US populations will in some cases make sense; and that the recruited populations should share the main characteristics of the eventual target groups for Phase 3 and beyond. Thus, we will focus only on the main components of trial design, which will, of course, be affected by HIV incidence and will, in turn, affect and be affected by trial sample size. These components are (1) control arms, (2) trial duration/duration of follow-up, (3) strength of evidence and level of effectiveness, and (4) adherence and its measurement.[23]

## Control Arms

Randomized controlled trials of new drugs are classically blinded and commonly include randomization of participants to either drug or inactive product (placebo) to control for observer bias and differential behavior. In the case of microbicides, a completely inactive or "inert" placebo remains to be identified. For example, a placebo might contain antimicrobial components in the form of preservatives or charged jelling agents, have an acidic pH disfavoring infection, provide lubrication reducing physical trauma to the mucosa, or act as a physical barrier to infection by coating the mucosa, thus producing some kind of protective effect in itself. Considerable work has been done to develop a placebo that would minimize the potential for protective effect, as reported in regulatory submissions in preparation for HPTN 035. Alternatively, a placebo might have some harmful effect, though this is speculative and believed highly unlikely for the hydroxyethyl and methyl cellulose gels that have been specially developed for trial use as part of ongoing efforts to minimize any possible protective effect. Some trial designers propose that this "placebo problem" can be circumvented by using a condom-only (no-treatment/no-product) arm so that the HIV rate in the microbicide arm may be compared directly with the baseline rate in that population.

The question here is whether a condom only/no-product arm is essential in effectiveness trials of topical microbicides. Further questions would have to do with the circumstances under which such a control arm could be dropped in the course of a given trial and whether such a control would be necessary for every tested product.

***STRENGTHS.*** Comparison of placebo (P) and condom-only (C) can provide a valid estimate of the effects of a placebo, assuming that behavior (i.e., condom use and other risk-taking behavior) remains independent of group assignment. Comparison of active treatment (T) and condom-only (C) can provide an estimate of the combined effect of microbicide use plus behavioral changes due to availability of microbicides, i.e., an estimate of "real world" or "use-effectiveness".

***LIMITATIONS.*** By definition, a condom-only arm cannot be blinded. This means that differences in HIV rates, in whichever direction (protection or potentiation), may be due as much to different risk behaviors as to the direct biological effect of the product, even though participants are told that the effectiveness of the microbicide is unknown. Some have argued that it is not necessary to understand the basis of any observed difference in HIV rates between arms as long as the situation reflects "real life". But a comparative study of treatment against condom-only does not reflect real life: when the microbicide comes to market, there will be no informed consent procedure, no regular safer sex counseling, and no clinical trial ethos to influence user risk behavior. The arguments laid down under "Strengths" above can be seen as essentially contradictory and requiring of contradictory assumptions. Comparing P to C requires the assumption that the associated behaviors do not differ, whereas in comparing T to C ("use-effectiveness"), we are allowing for the fact that behaviors might, in fact, differ.

It is also not certain that enough women can be motivated to possible randomization to a condom-only arm and comply with the protocol for the full length of the trial, including regular clinic visits for blood tests, etc., since the inducement of receiving product/placebo would not pertain. The differential in inducement raises an ancillary question: those who advocate for inclusion of a condom-only control have alluded to use of self-reported data to compare risk-taking behaviors across groups although, as observed later in this document *(see section on Adherence)*, our methods for assessing such behaviors remain limited. An unblinded control arm for which a core incentive to participants (i.e., access to test product) is lacking imposes further complexity on behavioral assessment that is now—and may remain—imponderable. Finally, the possibility of heavy losses to follow-up in a no-product arm could introduce significant bias if, for example, dropouts tended to be those who found condom use difficult or thought themselves more or less likely to have been infected.

***RECOMMENDATION:*** **The Subcommittee believes that the additional data a condom-only arm might furnish are likely to include more noise than useful information, may be uninterpretable, and could lead to erroneous conclusions about the products being evaluated. While there is no intent to imply that cost savings should take precedence over good science, we contend that cost savings resulting from the elimination of a condom-only arm might be better invested in increasing the power of the product and placebo arms and, possibly, Phase IV studies as more accurately reflective of "real-world" effectiveness. Still, we understand that there is considerable commitment to including a condom-only/no-treatment arm in the forthcoming HPTN 035 trial of PRO2000/5 and BufferGel. We recognize that the findings from the HPTN 035 trial could influence future regulatory policy, but argue that until those findings become available, which could be several years away, it would be unwise to lock in a regulatory requirement for a no-treatment arm. Given the implications of such an arm for sample size, recruitment, follow-up, costs in time and resources, and questions about generalizability to other candidate products, we therefore urge a highly flexible position with respect to inclusion of a condom-only arm in future effectiveness trials.**

## Trial Duration/Duration of Follow-up

The question here is: how long should participants be followed in Phase II and III trials of microbicides? Our understanding is that the FDA is looking for periods of on-treatment evaluation of 12-24 months, with all participants treated until the last recruit enrolled has completed 12-24 months of treatment. We do not know FDA's thoughts about duration of off-treatment follow-up.

***STRENGTHS.*** Longer duration of follow-up permits accumulation of more person/years of safety data and efficacy endpoints in conjunction with chronic use of product over time. This theoretically permits smaller sample sizes, in itself a benefit in terms of costs and logistics. Longer studies would also be advantageous if rates of sero-conversion were uneven over time, since such variability would be more likely to be captured; however, field experience to date has found that such rates are steady, so that there would seem to be no particular advantage to a longer period of follow-up if this is a desired objective.

***LIMITATIONS.*** With longer periods of follow-up, adherence may decrease with respect to both product use and clinic attendance, for a variety of reasons, including real and perceived side effects, withdrawals for pregnancy, and simply participant fatigue. Large loss to follow-up compromises study power almost by definition, can erode data quality as well as quantity, and may have an overall negative effect on study reliability and consequent regulatory assessment. Large losses to follow-up can also lead to bias if the reasons for the losses differ between study arms; they might also lead to an amount of variability across multiple trial sites that could be confounding.

***RECOMMENDATION:*** **The Subcommittee appreciates the desire of the FDA to capture as much data on putative product toxicity as possible. There is, nevertheless, no "magic time" that could unimpeachably predict toxicity, particularly against the background of extremely high risk that characterizes HIV-pandemic countries. Consideration is being given to trial designs in which the required woman-years of participation are achieved by enrolling a substantially larger number of women (perhaps requiring more**

**trial sites) who are followed for a shorter time, e.g., 6 months. The logistical and cost implications of a strategy requiring a large overall number of recruits to get the same reliability would be partially offset by the larger numbers needed for studies with longer follow-up which need to compensate by "over-recruiting" to account for drop-outs and withdrawals. Expectations from this temporal compression are that losses to follow-up and any consequent biases would be significantly smaller. Longer-term safety and acceptability data would be derived from sites where longer follow-up of good quality proved feasible.**

**We believe that such approaches offer a defensible balance between the ideal and the practicable, and propose a period of on-treatment evaluation of no more than 12 months per participant. We note that the potential for advance understandings about post-licensure surveillance studies has not been adequately explored and urge such exploration. Finally, we suggest scrutiny of the strategies employed in studies of contraceptive safety and effectiveness as a possibly informative analogue.**

## Strength of Evidence and Level of Effectiveness

The question here is: What minimum level of effectiveness should a Phase III microbicide trial aim to demonstrate, and with what degree of confidence? (We note parenthetically that in pursuing answers to that question, it is important to define what we are talking about. A Phase III microbicide trial does not measure the product's *efficacy*, i.e., its innate anti-infective potency, but rather its *effectiveness* in reducing the infection rate when used *as it was in that particular trial*. It may be that more consistent use in "real life" subsequent to the trial might well result in even fewer infections.)

Results from two adequate and well-controlled Phase III trials, each independently convincing ($p$: 0.05 x 0.05 = 0.0025), are generally required by the FDA to establish product effectiveness for licensing approval. Nonetheless, FDA has indicated that it would consider approving a microbicide on the basis of a single, large, multi-center, well-designed, and well-executed Phase III trial.[24] For such a trial, a one-sided $p$ value of 0.000625 (0.025 x 0.025, 0.001 two-sided) has been mooted, with the objective of showing significance at the same level as from two independent studies. There are, however, indications that the FDA might consider a value between 0.001 and 0.01, assuming that key criteria for study quality were met.

***STRENGTHS:*** Obviously, the $p$ value articulated above offers greater likelihood of licensure based on the results of a single trial. As for level of microbicide effectiveness, most product developers would regard an effectiveness level of about 33% (one-third fewer infections in the microbicide arm than in the control arm) as the minimum acceptable, in the belief that anything lower would be of dubious practical value. Furthermore, the number of women required, and hence the trial's practicability and costs, would increase dramatically to detect a lower effectiveness with the same degree of confidence. In any event, if a trial designed to detect 33% effectiveness were to actually show greater protection, say 50-60%, confidence in the result would be correspondingly greater.

***LIMITATIONS:*** We offer just one example of the potential implications of the $p$ value stipulated above, in association with a 33% effectiveness level. In a population with 2% annual HIV incidence, a two-arm trial with 2 years of follow-up and 90% power to detect 33% effectiveness at this significance level would require approximately 28,000 woman-years of data, or 7,000 women in each arm ─ a challenging target with heavy budgetary implications if we accept prevailing estimates of a per-volunteer cost of from US$3,500 to $5,000. Arguments that have been made against attempting such a trial have been predicated on feasibility, in turn predicated on implications for site number and capacity, recruitment potential, and costs.

***RECOMMENDATIONS:*** **The consensus of the Subcommittee is that we are in what is essentially a data-free zone with respect to decisions about the intertwined variables of level of effectiveness, strength of evidence, trial duration, and number of control arms. We respectfully ask the Advisory Committee to examine the table of alternative design scenarios prepared by the HPTN 035 protocol team, which is provided as an *Appendix* to this document, and to scrutinize its various implications. The table is based on a 33% effectiveness target, but consideration is being given by some product sponsors to a 50%**

**effectiveness level. Since the 33% level is presently theoretical and there is as yet no basis for arguing too hard one way or the other, we submit that this is another area where regulatory flexibility would be appropriate. We observe that elimination of the condom-only/no-treatment arm and shortening the period of follow-up (even accounting for the concomitant sample size increases mentioned earlier) could produce savings in time and costs that need not compromise the essential quality of microbicide effectiveness trials, particularly given the acute public health need which motivates them. As the closest example, the HPTN 035 trial, we vigorously urge that the AVAC question what is to be defined as a "win"[25] for the microbicides being tested. Is it essential that the product in question "beat" both a placebo and a no-treatment/condom-only arm, or might a victory over the former (perhaps with the other going in "the right direction", assuming interpretability), be sufficient, and how might "beating" and "sufficient" be defined?**

## Adherence

Admittedly limited experience in the trials of COL-1492 informs us that within a multi-site microbicide trial, as noted above, any observed differences in effectiveness among sites may be due, at least in part, to different adherence levels.

***STRENGTHS.*** Trustworthy information about adherence during a trial is relevant both to interpreting results and formulating claims about the product's protectiveness, and high confirmed levels of product use during Phase III will be critical to obtaining product registration. We believe that it is useful for regulators to be aware that behavioral research and trial experience have accumulated and advanced over the last few years in quantity and quality. It is reasonable to expect improvement in existing approaches (e.g., coital logs, diaries, questionnaires, and in-depth interviews) and/or their replacement with more rewarding techniques that could inspire greater confidence in trial results.

***LIMITATIONS.*** Nonetheless, there is yet no "true" measure of product adherence, since in microbicide trials it is understandably difficult to obtain invariably reliable feedback from participants on sexual behavior and microbicide and condom use.

***RECOMMENDATION:*** **This is not a recommendation to the Advisory Committee but, rather, an acknowledgment for its information. Despite deepening understanding about what behavioral research can produce in the way of microbicide trial quality and reliability, the Subcommittee agreed that the field has work to do with respect to learning from other drug trials about protocol adherence, and that efforts dedicated to promoting adherence to product use are as important and urgent as research aimed at developing microbicides with greater potency.**

## HPTN 035 Design Scenarios, 33% Targeted Effectiveness

| Option | Active Product Arms | Control Arms | Power | Final 2-sided p value | Non-US Person-Years* | Non-US Sample Size** | Yrs | No. of Mos. | Total Costs |
|---|---|---|---|---|---|---|---|---|---|
| 1a | 1 | 1 | 80% | 0.05 | 4810 | 2749 | 1.75 | 21 | 23,088,000 |
| 1b | 1 | 1 | 80% | 0.005 | 8158 | 4662 | 1.75 | 21 | 39,158,400 |
| 1c | 1 | 1 | 90% | 0.05 | 6439 | 3679 | 1.75 | 21 | 30,907,200 |
| 1d | 1 | 1 | 90% | 0.005 | 10244 | 5854 | 1.75 | 21 | 49,171,200 |
| | | | | | | | | | |
| 2a | 1 | 2 | 80% | 0.05 | 6764 | 3865 | 1.75 | 21 | 32,467,200 |
| 2b | 1 | 2 | 80% | 0.005 | 11472 | 6555 | 1.75 | 21 | 55,065,600 |
| 2c | 1 | 2 | 90% | 0.05 | 9054 | 5174 | 1.75 | 21 | 43,459,200 |
| 2d | 1 | 2 | 90% | 0.005 | 14405 | 8231 | 1.75 | 21 | 69,144,000 |
| | | | | | | | | | |
| 3a | 2 | 1 | 80% | 0.05 | 7730 | 4417 | 1.75 | 21 | 37,104,000 |
| 3b | 2 | 1 | 80% | 0.005 | 13111 | 7492 | 1.75 | 21 | 62,932,800 |
| 3c | 2 | 1 | 90% | 0.05 | 10348 | 5913 | 1.75 | 21 | 49,670,400 |
| 3d | 2 | 1 | 90% | 0.005 | 16463 | 9407 | 1.75 | 21 | 79,022,400 |
| | | | | | | | | | |
| 4a | 2 | 2 | 80% | 0.05 | 9620 | 5497 | 1.75 | 21 | 46,176,000 |
| 4b | 2 | 2 | 80% | 0.005 | 16316 | 9323 | 1.75 | 21 | 78,316,800 |
| 4c | 2 | 2 | 90% | 0.05 | 12878 | 7359 | 1.75 | 21 | 61,814,400 |
| 4d | 2 | 2 | 90% | 0.005 | 20488 | 11707 | 1.75 | 21 | 98,342,400 |

*Assuming 5.67% annual HIV-1 incidence in the placebo and no treatment arms and 81% annual retention rate.

**Assuming average follow-up time of 21 months.

# ALLIANCE FOR MICROBICIDE DEVELOPMENT

## Subcommittee Convened *Ad Hoc*
## To Prepare for FDA/CDER AVAC Meeting, 20 August 2003

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[14] This terminology originated in the 1993 CIOMS[14] *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, which stated that the first Phase I trial of any pharmaceutical product should be conducted in the country where that product was developed and manufactured, referred to as the "country of origin." The guideline was motivated by concerns about the exploitation of volunteers implicit in the testing in developing-country sites of drugs that would primarily benefit developed-country populations (termed "countries of use"). It was modified in the 2001 revision of the *Guidelines*, largely in deference to the realities of HIV/AIDS and the disparities between developed and developing countries with respect to burden of disease.

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